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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,639	VICKERS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-119* is/are rejected.

7)☒ Claim(s) *110 and 111* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-3-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 11-13-07.

Claims 108-119 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-13-07 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments with respect to previously pending claims have been considered but are moot in view of the new ground(s) of rejection set forth below.

Maintained Rejections

Claim Objections

Claims 110 and 111 are objected to because of the following informalities: The claims recite the misspelling "internulceoside." Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 108-119 are rejected under 35 U.S.C. 102(e) as being anticipated by Damha et al.

Damha et al (US 2005/0142535) teach the incorporation of modified residues into oligonucleotides, including 2'-modifications such as fluoro-, deoxy, alkoxy groups, including where the oligomer is uniformly modified with 2'-fluoro modificiations, and at least one or optionally each linkage is a phosphorothioate internucleotide link, or which modifications occur in various configurations and patterns, and which oligonucleotides

are between 12-30 nucleotides in length, and comprise a 5' terminal phosphate. Damha also teach the routine testing of these variously modified oligonucleotides for their ability to elicit RNAse H cleavage in human or animal target cells (see pages 1-2 (esp. paragraph 0111), 4-7, claim 38).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 108-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of McKay et al (USPN 6,133,246), Lima et al (Biochem., Vol. 36, pages 390-398, 1997), and Elbashir et al, Cook et al (US 2007/0032446) and Damha et al (US 2005/0142535).

The claims are drawn to methods of eliciting cleavage of target RNA in a human or animal cell comprising contacting the cell with an oligonucleotide between 12-30 nucleotides in length, which oligonucleotide comprises a 2'-fluoro modification on each nucleoside, and at least one, or optionally each internucleoside linkage is a phosphorothioate linkage, and which oligonucleotide comprises a 5' terminal phosphate.

McKay et al (USPN 6,133,246, 10-17-00) teach compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified sugar moieties including 2'-O-alkyl and 2'-fluoro sugars, and wherein the antisense optionally comprises various configurations of these modifications. McKay et al also teach the in vitro inhibition and routine screening of modulators comprising various configurations of modifications for their ability to target and inhibit expression of mRNA in vitro (see esp. col. 6-12).

Lima et al (Biochem., Vol. 36, pages 390-398, 1997) teach methods of modifying oligonucleotides, including incorporating phosphorothioate internucleotide linkages and 2'-Fluoro-modified sugars into oligonucleotides, and determining the effects of incorporating these modifications, in various configurations, on the stability of oligonucleotides from degradation, and on the effect of various configurations of phosphorothioate and 2'-Fluoro- modificiations on the oligonucleotides on the binding affinity and catalytic rate of RNAse (H1) (see the abstract and introduction on pages 390-1; Table 1 on page 393, text on pages 397-8).

Elbashir et al (EMBO J., Vol. 20, No. 23, pages 6877-6888, 2001) teach that SiRNA molecules comprising duplexes of 21 nucleobases and further comprising 2 nt 3' overhangs were most efficient triggers of mRNA degradation, and that substitution of siRNA strands with 2'-O-methyl abolished cleavage, but that substitutions of 2'-deoxynucleotide substitutions at the 3' end of the siRNA were tolerated. Elbashir provides a rational approach to the routine optimization of siRNA molecules for eliciting target mRNA cleavage, including the testing of incorporation of routine oligonucleotide modifications for siRNA optimization (see esp. the abstract; text in right hand col. On p. 6878; fig. 1 on p. 6879; fig. 2 on p. 6880; text on pp. 6880-6884; fig. 4 on p. 6882 and fig. 7 on p. 6884).

Cook et al (US 2007/0032446) teach methods of modifying oligonucleotides, including incorporating phosphorothioate internucleotide linkages and 2'-fluoro-modified sugars into oligonucleotides, and determining the effects of incorporating these modifications, in various configurations, on the binding affinity and catalytic rate of RNAses (see esp. pages 1-6, claims 49, 50 and 52).

Damha et al (US 2005/0142535) teach the incorporation of modified residues into oligonucleotides, including 2'-modifications such as fluoro-, deoxy, alkoxy groups, and phosphorothioate internucleotide linkages, in various configurations and patterns, and testing these variously modified oligonucleotides for their ability to elicit RNAse H cleavage (see esp. pages 1—2, 4-5, 7).

It would have been obvious to screen various antisense oligonucleotide molecules for their ability to elicit cleavage of a known target gene, either through an

SiRNA or RNAse mechanism, and which oligonucleotides comprise various modifications and configurations, including those instantly claimed because it was well known in the art, as taught by McKay et al, Lima et al, Elbashir et al, Cook et al and Damha et al, that the incorporation of various modifications including incorporation of 2'-O or 2'-Fluoro modifications, phosphorothioates, enhance oligonucleotide stability, target cell uptake, target binding and/or target gene cleavage, and the particular configuration would require routine screening as taught previously by these references.

It has been standard operating procedure for laboratories to design modifications configurations for antisense oligonucleotides, then assay them for stability, target binding and eliciting SiRNA or RNAse cleavage, as taught previously by McKay et al, Lima et al al, Elbashir et al, Crooke et al, Cook et al and Damha et al. One of ordinary skill in the art would have expected that the incorporation of these modifications would provide for either higher affinity for a target gene, enhanced oligonucleotide stability from non-specific nucleases, and/or enhanced cleavage of target genes, and to test for optimal configurations would be routine experimentation to one of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to elicit cleavage of a target mRNA of known sequence to inhibit its expression, because Lima, Cook, Damha and Elbashir all teach the routine experimentation involved in assessing the ability of variously modified oligonucleotides to elicit cleavage of or inhibit expression of a known target gene using variously modified antisense or SiRNA oligonucleotides. One of ordinary skill in the art would

have been motivated to utilize such methods previously taught for finding optimal oligonucleotides between 12-30 nucleobases which best target and inhibit target gene expression, including upon elicitation of cleavage, in order to study a target molecule's role in the various associated cellular processes, or as a possible therapeutic agent, or to study its role in related pathologies and one would be motivated to study how these processes are regulated by the target gene. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense or SiRNA oligonucleotides for inhibiting a target gene of known sequence, including by RNAse H cleavage, because these methods of modifications and assessment of inhibitory activities were taught previously by many, including McKay et al, Lima et al al, Elbashir et al, Cook et al and Damha et al, which techniques were considered to be routine for a previously characterized target gene, and which techniques would successfully be used to identify numerous antisense oligonucleotides or SiRNA for the elicitation of cleavage and inhibition of target gene expression.

One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, or chimeric, or alternating or completely modified residues, into antisense or siRNA oligonucleotides because such modifications (e.g. 2'-O-methoxyethyl, 2'-fluoro and phosphorothioate linkages) have been taught previously by McKay et, Damha, Cook, Lima, Elbashir and others to increase target binding, cellular uptake and/or oligonucleotide stability. One of ordinary skill in the art would have expected that the delivery of modified oligonucleotides to target cells harboring target genes of interest, which antisense specifically hybridize with

the target mRNA, would lead to inhibition of expression of the target gene, including by eliciting RNAse cleavage in the cell.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
1-31-08

J Zara TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER